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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,519	09/26/2003	Thais Motria Sielecki-Dzurdz	PH-7407 NP (BMS-2364)	6480

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/670,519	SIELECKI-DZURDZ ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-51 and 55-68* is/are rejected.

7)☒ Claim(s) *52-54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/29/03&3/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on 9/26/03. There are sixty-eight claims pending and sixty-eight under consideration. Claims 1-55 are compound claims. Claims 55 and 56 are composition claims. Claims 57-68 are method of using claims. This is the first action on the merits. The application concerns some hetero fused pyrazinone compounds, compositions, and uses thereof.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "symptoms caused by elevated levels of corticotrophin releasing factor", "stress–related symptoms" or "a disorder characterized by abnormal levels of corticotrophin releasing factor". It is unclear what diseases and treatments applicant is intending to encompass. Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the

patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite. There is an impressive list of such conditions found in paragraphs [00058] and [00059] on pages 25 and 26 of the specification. However, this list uses open language. In addition to this multitude of diseases, for which other diseases is treatment being claimed?

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-51 and 55-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making either prodrugs or radiolabel forms of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or

unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found in paragraph [0052], page 24. c) There is no working example of a prodrug of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. The table on the left side of

page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula (I) as well as the presently unknown list potential prodrug derivatives embraced by claim 1.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

4. a) Each radioisotope label will require a different synthetic method. Considering the number of possible radioisotopes, the differing sites where these labels may be placed, and the number of molecules to be made this is a very large quantity of experimentation. b) The direction concerning the radio-labeled compounds is found in paragraph [0053], page 24. No labeled starting materials are taught. c) There is no working example of a radio-labeled form of a compound the formula (I). d) The nature of the invention is chemical synthesis using radioactive staring materials. e) Evans (Principles of Radiopharmacology) says in the first sentence, second paragraph, page 11 "[i]sotopic labeling with carbon-14 ... provides a challenge to the ingenuity of the biochemist or organic chemist." In the third sentence, second paragraph, page 13 he says "[c]hemical syntheses for the

preparation of [^{14}C] compounds are normally multistage". In the first sentence, last paragraph page 24, he concludes "labeling with carbon-14 and with tritium continues to provide interesting, challenging and exciting opportunities for the biochemist and organic chemist". These three passages make clear that preparing any specific [^{14}C] compound is not a matter of routine experimentation, is not certain of success, and can challenge the most highly skilled synthetic chemist.

In the first two sentences on page 13 Evans (Principles of Radiopharmacology) says "chemical synthesis, biochemical methods ... are especially important for the preparation of carbon-14 compounds". In the fifth line from the bottom of page 13 he says "[t]he labeled atom is usually derived from barium [^{14}C] carbonate or from [^{14}C] carbon dioxide as raw materials."

Applicants' in their disclosure on page 24 do not disclose the use of either of these two raw materials for the synthesis of their molecules. There are two art recognized starting materials for [^{14}C] compound synthesis. Applicants have failed to disclose any process for converting those two into any of their claimed compounds. f) The artisans making Applicants' radio-labeled forms would be synthetic pharmaceutical chemists. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors

involved", and chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula (I) as well as the approximately 5,000 known natural and artificial radioisotopes. Thus, the breadth of the claims is broad. Some of these have long half-lives and emit relatively low energy radiation so that routine laboratory equipment may be used to make the labeled compounds from them. Some of them have half-lives measured in the seconds and emit extremely high-energy radiation as they decay. For these, the isotopes must be generated in the facility where they are to be used and very specialized shielded equipment must be used to handle them.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make any particular radio-labeled form.

The Examiner suggests deleting the phrase "or prodrug thereof or radiolabeled form there of".

5. Claims 57-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating anxiety, does not reasonably provide enablement for treating "symptoms caused by elevated levels of corticotrophin releasing factor", "stress–related symptoms" or "a disorder characterized by abnormal levels of corticotrophin releasing factor". The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. The factors to be considered in making an enablement rejection have been summarized above. The three main issues are the lack of any correlation between clinical efficacy for "symptoms caused by elevated levels of corticotrophin releasing factor", "stress–related symptoms" or "a disorder characterized by abnormal levels of corticotrophin releasing factor" treatment and Applicants' two *in vitro* assays, the state of the prior art, and the breadth of the claims.

There is an *in vitro* assay, drawn to binding to the CRF_1 receptor, described in the passage spanning paragraph [00342] to paragraph [00344] with no data. Applicants do not state and it is not recognized in the clinical arts this assay is correlated to efficacy for treating the hundreds of different diseases embraced by

these claims diseases. There is an *in vitro* assay, drawn to inhibiting the activity of the CRF_1 receptor, described in paragraph [00346] to paragraph [00344] again with no data. Applicants do not state and it is not recognized in the clinical arts this assay is correlated to efficacy for treating the hundreds of different diseases embraced by these claims diseases.

Gutman (J. Pharmacol Exp. Ther.) provides the state of the pharmacological arts with CRF1 receptor antagonists. Gutman (J. Pharmacol. Exp. Ther.) in the final paragraph on page 879 that the CRF_1 receptor antagonist R121919 is active in a rat model of anxiety. Heinrichs (Neuropsychopharmacology) reports in Table 2, page 200 "Anxiolytic-like Efficacy of R121919". Habib (PNAS) reports reduced anxiety in a monkey model induced by the CRF_1 receptor antagonist Antalarmin in the final paragraph on page 6082.

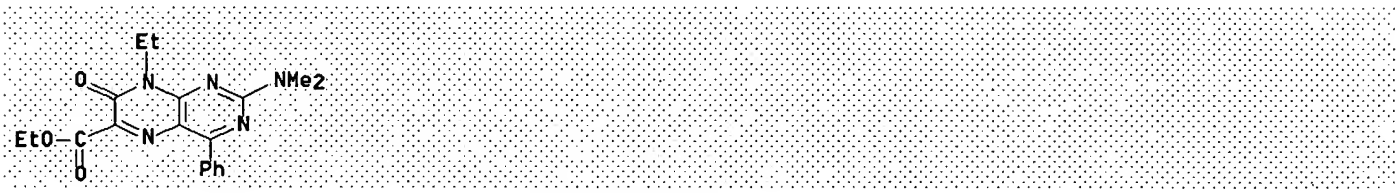
The scope of the claims involves all of the thousands of compounds of claim 1 as well as the unknown list of diseases embraced by the terms “symptoms caused by elevated levels of corticotrophin releasing factor”, "stress–related symptoms" or "a disorder characterized by abnormal levels of corticotrophin releasing factor". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the

time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Allowable Subject Matter

6. Claims 52-54 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The following is a statement of reasons for the indication of allowable subject matter: Applicants' claim 1 is patentable over Taylor (JOC). Taylor (JOC) teaches the 7,8-dihydro-7-oxo-4-phenyl-6-pteridinecarboxylic acid ethyl ester compound shown below. This compound has an R^1 group not presently claimed.



Conclusion

7. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private

for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

8. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

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TCMcK/me